REMARKS

In the Office Action, the Examiner rejected claims 1-20 under 35 U.S.C. § 112, second paragraph; rejected claims 1-20 under 35 U.S.C. § 112, first paragraph; rejected claims 1-20 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,219,895 to Kelman et al.; rejected claims 1, 5-10, 11 and 15-20 under 35 U.S.C. § 102 as being anticipated by U.S. Patent Application Publication No. US2002/0022588 to Wilkie et al.; rejected claims 1-3 under 35 U.S.C. § 102 as being anticipated by U.S. Patent No. 6,197,934 to DeVore et al.; rejected claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over Kelman et al., U.S. Patent No. 6,161,544 to DeVore et al. (hereinafter "DeVore '544", and U.S. Patent No. 6,495,127 Wallace et al.; rejected claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over Wilkie et al. in view of Kelman et al. and DeVore '544; rejected claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over DeVore et al. in view of Wilkie et al., Wallace et al., Kelman et al. and Devore '544; and rejected claims 1-20 under the judicially created doctrine of obviousness-type double patenting.

Applicants have amended claims 1, 5-8 and 10-12; cancelled claims 13-20; and added new claims 21 and 22. Claims 1-12, 21 and 22 are pending in the present application.

By way of background, Applicants' disclosure is directed toward, among other things, a novel method of making a new tissue adhesive composition. Tissue adhesives or solders must have

sufficient mechanical properties to strongly join tissues in surgical applications (see Applicants' specification at page 1, lines 8-9). Tissue adhesives should also be non-toxic (id., lines 10-14). In laser-assisted welding applications disclosed herein, tissues are joined together, the adhesive is applied, melted, and as it cools and solidifies, the tissues are bonded together.

Applicants' novel tissue adhesive satisfies the above-described requirements of tissue adhesives. The composition is collagen based, and is therefore non-toxic. Moreover, the inventive adhesive has a high concentration of derivatized collagen (which is also gelatinized (page 10, line 20 - page 11, line 5)), and is believed to provide a greater number of linkages so that upon exposure to laser light of a suitable wavelength, increased crosslinking with surrounding tissue is believed to occur (specification at page 3, lines 1-3; page 4 lines 3-5). Accordingly, a tissue adhesive having improved cohesive strength and exceptionally strong tensile strength of 1000g/cm^2 can be achieved (specification at page 14, lines 20-21). By attaching carboxyl and carboxyl/thiol groups to the collagen through derivatization, it is believed that the collagen has a net negative charge, potentially allowing the adhesive to ionically interact with the positively charged proteins in tissues. In addition, deriviatization in accordance with the present invention renders the adhesive soluble at physiologic pH (page 9, lines 8-11), and the adhesive will dissolve in the body over time.

Applicants realized, however, that derivatized collagen solutions saturate at about 10% or 10 mg/ml (see page 10, lines 15-16), far short of the concentration believed necessary to provide a sufficient number of cross-linking tissue bonding sites, as noted above. In light of the limited solubility of known derivatized collagen-based solutions, Applicants developed a unique process to make their novel tissue adhesive. As described in the specification and recited in amended claim 1, collagen is derivatized with a carboxyl (COO^-) functional group, for example (page 9, lines 17-19; page 10, lines 6-8), and a solution of the derivatized collagen is formed (see, for example, the specification at page 10, lines 16-20 "lyophilized or powdered collagen preparations in 0.02 M phosphate buffer at pH 6.8-7.8 [were mixed]. Mixtures of approximately 50 mg/ml were initially prepared", page 10, lines 18-20).[1] The solution is heated to thereby gelatinize the derivatized collagen (see, for example, the specification at page 10, lines 18-20, "[m]ixtures of approximately 50 mg/ml were initially prepared and exposed to thermal energy, in this case microwave energy ... [m]icrowave energy generates thermal energy causing the gelatinization of collagen."), and carboxyl-derivatized collagen was added to the solution (see, for example, the specification at page 9, line 20-page 10, line 4; and page 10, lines 22-23 "lyophilized or dried collagen was added to the gelatinized collagen solution and again

[1] References to "collagen" at page 10 of Applicants' specification, for example, refer to collagen derivatized with either carboxyl or carboxyl and thiol groups as described in the preceding pages of the specification, e.g., page 9.

exposed to microwave energy"). The heating and adding steps are repeated until the concentration of said derivatized collagen in said solution is from 300 mg/ml (30%) up to 800 mg/ml (80%) (see, for example, the specification at page 10, lines 15-16 and page 10, line 23 - page 11, line 1 "[t]his sequence continued until the desired collagen concentration was attained."). The added derivatized collagen is also gelatinized after the repeated heating steps (see, for example, the specification at page 10, lines 20, "[m]icrowave energy generates thermal energy causing the gelatinization of collagen"; also page 11, lines 2-4 "[After the sequence of addition and heating,] gelatinized collagen [was poured into molds").

Applicants' changes to claims 6, 8 and 11-13 are also adequately supported by the specification. Amended claim 6 requires a further step of derivatizing the collagen with a thiol (SH^-) group (see, for example, specification at page 10-lines 6-8 and page 9, lines 2-12). Amended claim 8 depends from claim 1 and further requires that the solution be deaerated, and is deemed to be supported by the specification, for example, at page 11, lines 1-2 and page 17, lines 15-19. Amended claim 11 depends from claim 1, and further recites a step of solidifying the solution, support for which may be found in the specification, for example, at page 11, lines 4-5. Amended claim 12, depends from claim 11, and further requires a step of sectioning the solidified solution into strips. Support for amended claim 12 may be found in the specification, for example, at page 11, lines 4-5.

Claim 7 has been amended to further define the pH of the solution within a range of 6.8-7.8, subject matter recited in original claim 8. Also, claim 10 has been amended to maintain antecedent basis.

New claim 21 requires that the added carboxyl-derivatized collagen is dried, and new claim 22 recites that the added carboxyl-derivatized collagen is lyophilized. Support for new claims 21 and 22 can be found in the specification, for example, at page 10, lines 16-20 (noted above).

Accordingly, Applicants respectfully submit that their claim changes are adequately supported by their disclosure.

Applicants respectfully traverse the Examiner's rejections of claims 1-20 under 35 U.S.C. § 112, second paragraph. At the outset, Applicants respectfully submit that this rejection, as well as other rejections contained in the Office Action are moot with respect to cancelled claims 13-20.

The Examiner contends at page 2 of the Office Action that "it is unclear what is contemplated within the meaning of 'functional group'". Applicants respectfully note that the Examiner's rejection with respect to claim 11 is moot in light of the amendment of this claim. Applicants also respectfully point out that claim 1, as amended, recites a step of derivatizing collagen with a COO^- (carboxyl) group. Support for claim 1 is discussed above. Applicants' amendment to claim 1 should resolve any alleged ambiguity as to the identity or the meaning of the derivatizing functional group.

At page 3 of the Office Action, the Examiner asserts that "[i]t was not found in the specification where the functional groups in question were to be attached within the collagen molecule." Applicants respectfully disagree.

The specification at page 10, lines 6-10 states:

> Base compositions contained either COO^- functional groups or both SH^- (thiol) and COO^- functional groups. The degree of derivatization with SH^- functional groups was varied in attempts to modulate cohesive characteristics. Remaining free amine groups on the native collagen molecule were derivatized with COO^- groups.

Emphasis added.

This cited portion of the specification expressly describes that derivatization occurs at the location of free amine groups on the native collagen molecule. Thus, the specification does indeed describe where carboxyl and thiol groups are attached during derivatization.

Applicants have amended claim 5 to clarify its dependency from claim 1, and to correct a typographical error pointed out by the Examiner at page 3 of the Office Action.

In light of Applicants' amendment to claim 11, and cancellation of 16, Applicants respectfully submit that the Examiner's objections to these claims, as discussed at pages 3 and 4 of the Office Action, are moot. Applicants also respectfully submit that the Examiner's objection to use of the term "adjust" in claim 6 is also moot in light of Applicants amendment to this claim.

Accordingly, in light of the amendments discussed above, Applicants respectfully request the Examiner to reconsider and

withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Applicants respectfully traverse the Examiner's rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph. Although Applicants respectfully disagree with the arguments set forth by the Examiner in formulating the rejection under § 112, first paragraph, Applicants appreciate the Examiner's comments, and have made various claim changes in light of the Examiner's proposals.

In particular, Applicants have amended claim 1 to recite a method of making a tissue adhesive, as suggested by the Examiner at page 5 of the Office Action.

As noted above, Applicants have also amended claim 1 to recite a step of heating a solution including collagen derivatized with a carboxyl group. Accordingly, the Examiner's objection with respect to the scope of the originally filed claims is deemed to be moot.

In addition, Applicants respectfully point out that the specification is not only directed toward formulations having collagen derivatized with both carboxyl and thiol groups. Rather, derivatization with carboxyl groups without thiol groups is expressly described in the specification at page 10, lines 6-8 ("Solder formulations were prepared from chemically derivatized Type 1 collagen. Base compositions contained either COO^- functional groups or both SH^- (thiol) and COO^- functional groups."; see also page 10, line 10: "Base preparations contained only COO^-)groups".) The specification thus provides support for collagen compositions including collagen derivatized with carboxyl

groups, as well as carboxyl groups with thiol groups.

Applicants have also amended claim 1 to further define a range of concentrations "is from 300 mg/ml (30%) up to 800 mg/ml (80%)" consistent with the Examiner's proposed claim language at page 8 of the Office Action.

Applicants have also incorporated pH ranges recited in claim 8 into amended claim 7, as also suggested by the Examiner (see Office Action at page 9).

Accordingly, Applicants respectfully submit that pending claims 1-13 meet the requirements of 35 U.S.C. § 112, first paragraph.

Applicants respectfully traverse the Examiner's rejection of claims 1-20 under 35 U.S.C. § 102(b) as being anticipated by Kelman et al.; rejection of claims 1, 5-10, 11 and 15-20 under 35 U.S.C. § 102 as being anticipated by Wilkie et al.; rejection of claims 1-3 under 35 U.S.C. § 102 as being anticipated by DeVore et al.; rejection of claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over Kelman et al., DeVore '544, and Wallace et al.; rejection of claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over Wilkie et al. in view of Kelman et al. and DeVore '544; rejection of claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over DeVore et al. in view of Wilkie et al., Wallace et al., Kelman et al. and DeVore '544"); and the rejection of claims 1-20 under the judicially created doctrine of obviousness-type double patenting.

Applicants respectfully submit that the Examiner's rejections

are moot in light of the amendments to claims 1 and 11, and cancellation of claims 13-20. Moreover, to the extent the Examiner's rejections are pertinent to amended independent claim 1, Applicants respectfully submit that none of the applied references teaches or suggests each and every step recited in the claim. In particular, the applied prior art at least fails to teach the claimed method including the steps of heating a solution including collagen derivatized with a carboxyl group to thereby gelatinize the derivatized collagen; adding derivatized collagen to the solution; and repeating the adding and heating steps until the derivatized collagen concentration in the solution is from 300 mg/ml (30%) up 800 mg/ml (80%), the added derivatized collagen in the solution being gelatinized after said repeated hearing steps.

As noted above, due to the known saturation limit of 100 mg/ml of collagen in solution, Applicants developed their claimed method in order to achieve higher concentration formulations. None of the cited references even addresses the problem associated with the saturation limit of collagen solutions. As discussed in greater detail below, Applicants' method of making high concentration carboxyl-derivatized collagen solutions is neither taught nor suggested by the applied prior art.

Specifically, although Kelman et al. describes acylation of collagen with glutaric anhydride, the resulting collagen is dissolved in a solution and exposed to ultraviolet light (see col. 7, line 64-col. 8, line 10). No further heating steps are performed, and neither is additional collagen added to the

solution to obtain the claimed concentration. Accordingly, the reference is entirely silent as to the claimed adding, heating and repeating steps, as recited in amended claim 1.

With respect to Wilkie et al., the Examiner contends that Example 5 at page 18 and the last sentence at page 6 of the reference discloses "derivatizing collagen (700 mg; 20-45%) with glutaric anhydride ... wherein the resulting solution may be titrated ... and may also be heated." (see Office Action at page 11). Wilkie et al. in Example 5 discloses adding 7 grams of collagen derivatized with "glutaric". Mere mention of "glutaric" does not necessarily imply glutaric anhydride, as other known chemicals may contain the term "glutaric" in their nomenclature, e.g., glutaric acid; glutaric aldehyde; glutaric ethers etc. Moreover, the derivatized collagen disclosed in Example 5 is simply added to a mixture of perfluorooctanoic acid; phosphate buffer and NaOH. Wilkie et al. clearly does not disclose claimed adding carboxyl-derivatized collagen to a solution containing carboxyl-derivatized collagen, heating the solution, and repeating the adding and heating steps to obtain the claimed concentration, as recited in amended claim 1.

Moreover, while Wilkie et al. discloses "20-45% derivatized collagen", Applicants submit that the described percentage defines an amount of derivatization of the collagen, but not a concentration of collagen itself, in units of mg/ml. Applicants further note that in Example 5, 7 grams of derivatized collagen are added to the buffered solution described above on a "100 g

scale" (see paragraph 0289) to obtain "a sealant composition based on 7% collagen". Accordingly, Example 5 only teaches adding 7 grams of derivatized collagen to a non-collagen solution to obtain a total of 100 grams of material having an overall concentration of 7%. In contrast, amended claim 1, as noted above, requires repeating heating and carboxyl-derivatized collagen adding steps to obtain a high concentration from 300 mg/ml up to 800 mg/ml. Wilkie et al. fails to disclose these steps.

Further, the teachings identified by the Examiner at page 6 of Wilkie et al. are only directed toward albumin compositions. There is no suggestion to apply such teachings to collagen-based adhesives. For example, the subject matter of claim 3 of Wilkie et al. (also identified at page 11 of the Office Action) is dependent from claims 1 or 2 of the reference. Both claims recite, in pertinent part, providing a protein with a surfactant and a lipid, as well as a "crosslinker" to bond tissue. Applicants fail to see how teachings of crosslinking and mixtures with lipids and surfactants relate, in any way, to the albumin discussion at page 6 of Wilkie et al. to thereby anticipate Applicants' claimed method. The claims of Wilkie et al., as well as the teachings at page 6, are devoid of any disclosure or suggestion of heating a carboxyl derivatized collagen solution, adding carboxyl-derivatized collagen to it, and repeating the heating and adding steps to obtain claimed concentration.

The Examiner further cites the second paragraph in the second column at page 3 of Wilkie et al. in support of the assertion

that collagen and fibrin "may be used for their bioadhesive or sealant properties of the cross-line [derivatized collagen]". Applicants respectfully note that cross-linked collagen is not necessarily derivatized. As noted in Applicants' specification, discussed above, derivatization with a carboxyl group involves attaching such a group to the collagen molecule, not crosslinking in which different protein strands of the molecule bind to each other. In any event, the cited portion of Wilkie et al. is solely directed toward albumin, and expressly states that solutions of albumin can "tolerate" the presence of collagen. Such teachings would suggest that small amounts of collagen can be include in the albumin solutions of Wilkie et al. The cited text of Wilkie et al. thus teaches away from Applicants claimed method of making a high concentration collagen, not albumin, adhesive.

Applicants also respectfully submit that comparisons between albumin and collagen are misplaced. First, due to the "highly unpredictable and complex nature of determining adhesive compatibility and capabilities" (see Office Action at page 4), Applicants respectfully submit that adhesive properties of carboxyl-derivatized and gelatinized collagen would not have been readily apparent to one of ordinary skill based upon albumin teachings. Albumin is a different material than collagen, its molecules are smaller than collagen's. Although viscous solutions of albumin are possible, high collagen solutions are not known due to the saturation of collagen at 100 mg/ml (specification at page 10, lines 15-16).

In formulating the Section 102 rejection based on DeVore et al. (U.S. Patent No. 6,197,934), the Examiner asserts that "Devore et al. teach heating [and additional heating] a derivatized [COO-] collagen (column 1, lines 44-47), to a pH of 7.4 (column 4, line 31) and the use of NaOH as a pH altering material (column 4, line 22). Applicants note, however, that the cited portion of DeVore et al. at column 1 only states a single derivatized collagen heating step, not repeated heating and carboxyl-derivatized addition steps, as required by amended claim 1. In any event, DeVore et al. discloses adding "a therapeutic compound" such as mitomycin, an anti-metabolic antibiotic, to the heated derivatized collagen (col. 1, lines 41-47, and 63-65), *not* carboxyl-derivatized collagen. Such disclosure also fails to teach the claimed heating, adding, and repeating steps, as recited in amended claim 1.

Moreover, whatever DeVore et al. does disclose about collagen concentration corroborates Applicants' discussion of the difficulty in achieving high concentration carboxyl-derivatized collagen solutions. DeVore et al. apparently discloses dissolved collagen in a solution having a "concentration of 10 mg/ml" (see col. 4, lines 29-33), well below the claimed concentration from 300 mg/ml up to 800 mg/ml, as recited in amended claim 1.

In light of the above-described deficiencies of Kelman et al., DeVore et al., and Wilkie et al., Applicants submit that amended claim 1 is not anticipated by any of the applied references. Moreover, claims 2-12 are allowable at least due to

their dependence from claim 1.

Turning to the rejections under Section 103, the Examiner contends that claims 1-20 are unpatentable over Kelman et al., DeVore '544 and Wallace et al., the Examiner contends that portions of Devore et al. ('544) teach use of 4-mercapto-1,8-naphthalic anhydride ("4-Mercapto"), and that claim 4, which recites reaction with the 4-Mercapto, is thus obvious (Office Action at page 12).

Devore et al.'544 lists 4-Mercapto, along with many other compounds, but the use of 4-Mercapto in the reference is entirely different than that of 4-Mercapto in Applicants' specification. Specifically, Devore et al. discloses 4-Mercapto as a "destabilizing agent" (col. 5, lines 32-35) for softening eye tissue ("In the methods to be described herein, chemical agents which soften, degrade or 'destabilize' the structural components of the stroma are topically administered to the cornea 10." Col. 4, line 66-Col. 5, line 2. Thus, Devore et al. teaches application of 4-Mercapto to tissue itself for the purpose of degrading or destabilizing the tissue. Such use is unrelated to derivatization of collagen of an adhesive for the purpose of gluing tissues. Accordingly, Devore et al. teaches away from Applicants claimed method including the step of further derivatizing a carboxyl-derivatized collagen with 4-mercapto, as required by claim 4.

Further, apparently with respect to claim 4, the Examiner also alleges that sulfonating agents can be used in connection

with thiol derivatization (Office Action at page 12). As generally understood, however, sulfonation denotes a sulfonic group (SO_3^{-1}), not an SH^-, i.e., thiol, group. If anything, Kelman et al. teaches derivatization of collagen with a sulfonic group, not a thiol group, as required by amended claim 6. Claim 6, therefore, is distinguishable over Kelman et al. at least for this reason as well.

The Examiner further relies on teachings in Wallace et al. of microfibrillar and fibrillar collagen in arguing that claims 10 is obvious as well. Applicants respectfully submit, however, that even if Wallace et al. were combinable with Kelman et al. and DeVore '544 in the manner proposed by the Examiner, the teachings of Wallace et al. would fail to overcome the above-described shortcomings of both Kelman et al. and DeVore '544.

With respect to the Examiner's rejection of claims 1-20 as being unpatentable over Wilkie et al. in view of Kelman et al. and DeVore '544, the Examiner apparently relies on alleged teachings of thiol derivatization in Kelman et al. and disclosure of 4-Mercapto in DeVore '544 in further arguing that claim 4 is obvious. As note above, however, Kelman et al. teaches sulfonating (derivatizing with a sulfonic or SO_3^{-1} group, not a thiol group, and DeVore '544 describes use of 4-Mercapto to degrade tissues, not further derivatizing a carboxyl-derivatized collagen, as recited in amended claim 4. Moreover, even if DeVore '544 were combinable in the manner proposed by the Examiner, the reference would fail to remedy the above-described deficiencies of

both Kelman et al. and Wilkie et al.

Amended claim 1, therefore, is not obvious over the Examiner's proposed combination of Kelman et al., DeVore '544, and Wallace et al., nor is claim 1 obvious Wilkie et al., Kelman et al., and DeVore '544. Moreover, claims 2-12 are allowable at least due to their dependence from claim 1.

With respect to the Examiner's rejection of claims 1-20 under 35 U.S.C. § 103 as being unpatentable over DeVore et al., Wilkie et al., Wallace et al., Kelman et al. and DeVore '544, each of these references has been thoroughly discussed above and neither one, taken alone or in combination, teaches or suggests Applicants' claimed method, as recited in amended claim 1 including the heating, adding and repeating steps. Accordingly, claim 1 is allowable over the Examiner's proposed combination of DeVore et al., Wilkie et al., Wallace et al., Kelman et al. and DeVore '544, and claims 2-12 are allowable at least due to their dependence from claim 1.

With respect to the Examiner's double patenting rejection, the Examiner asserts that claims 4, 17 and 24 of Kelman et al. in combination with "DeVore et al." (Applicants are unclear which of the two cited DeVore references the Examiner relies upon in the double patenting rejection) and Wallace et al. render claims 1-20 unpatentable. Claims 4, 17 and 24 are directed toward a collagen composition wherein Type 1 collagen is derived from human tissue or animal tissue (claim 4, which depends from claim 1); a method of making a collagen composition including steps of, in part,

preparing partially fibrillar collagen and reacting the partially fibrillar collagen with at least one of an acylating agent and sulfonating agent at a pH ranging from 7.5 to 10.0 and a temperature ranging from 4°C to 37° C (claim 17); and the method, in part, wherein the acylating agent is glutaric anhydride (claim 24, which depends from claim 23, which in turn depends from claim 17). None of these claims recites the claimed method of amended claim 1 including steps of heating a solution containing carboxyl-derivatized collagen; adding carboxyl-derivatized collagen to it; and repeating said heating and adding steps to obtain the claimed concentration. Since, as noted above, both Devore references and Wallace et al. also fail to teach or suggest the method recited in amended claim 1, Applicants submit that the claim is patentable over claims 4, 17 and 24 taken in combination either Devore reference and Wallace et al., and claims 2-12 are allowable at least due to their dependence from claim 1.

New claims 21 and 22 depend from claim 1 and further recite that the added derivatized collagen is dried (claim 21) and lyophilized (claim 22). As discussed extensively above, none of the prior art of record teaches or suggests Applicants' claimed method, as recited in amended claim 1, and certainly fails to teach or suggests the method recited in claims 21 and 22. Claims 21 and 22, therefore, are deemed allowable at least due to their dependence from claim 1.

Since Applicants have retained claim language related to derivatized collagen, Applicants submit that the independent

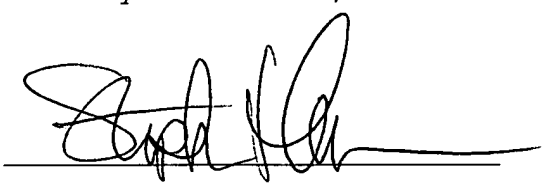
claims present in this application are not directed toward "substantially change[d] subject matter" (see Office Action dated November 19, 2003), to the extent this phrase is understood. Thus, in light of the foregoing amendment and remarks, Applicants respectfully entry of this Amendment, reconsideration and withdrawal of the outstanding rejections and objections, and a timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 02-0900.

PTO is authorized to credit any overpayment to our Deposit Account.

If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

By: 

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